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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/972,912	10/10/2001	Daniel R. Soppet	1488.0620003	5683

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EXAMINER	
ROMEO, DAVID S	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 03/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/972,912	SOPPET ET AL.	
	Examiner	Art Unit	
	David S Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,12 and 16-75* is/are pending in the application.

4a) Of the above claim(s) *10 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *10,12 and 16-75* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0112*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 11/21/2003 has been entered. Claims 10, 12, 16-75 are pending.

Applicant's election with traverse of group I and of the species I(c) in the paper filed 11/21/2003 is acknowledged. The traversal is on the ground(s) that there is no serious burden to examine groups I, II, and III together; that properly designed sequence searches would encompass all the related polynucleotide sequences; the parent application was restricted into only three groups, and the examiner has not provided any reasoning to explain why the search burden has changed in the present application; that all the species were examined as a single group in the parent application; that claim 1, instead of claim 3, is a more appropriate generic claim; that it is not clear to which species the examiner is referring at page 7, lines 7-8. This is not found persuasive because an application may properly be required to be restricted to one of two or more claimed invention if they are able to support separate patents and they are either independent (MPEP § 806.04 - § 806.04 (j)) or distinct (MPEP § 806.05 - § 806.05(i)). Groups I and II are distinct for the reasons given in the Office action mailed 10/23/2003. Furthermore, separate classification (i.e., class and subclass) of distinct inventions is sufficient to establish a prima facie case that the search and examination of the plural inventions imposes a serious burden upon the Examiner. See M.P.E.P. § 803. Such separate classification is set forth in the Office action mailed 10/23/2003. Polynucleotide and polypeptide searches are not coextensive as indicated by their separate classification. Applicant has offered no evidence to rebut this showing. Contrary to Applicants'

assertion that any search of the prior art in regard to group I will reveal whether any prior art exists as to the other groups, a search is directed to references which would render the invention obvious, as well as references directed to anticipation of the invention, and therefore requires a search of relevant literature in many different areas of subject matter. Applicant ahs indicated that a "properly designed search" would encompass all the related sequences, but Applicant has not indicated what this "properly designed search" might be. The examiner maintains that a search of something 95% identical to one thing is not the same as a search of something 95% identical to another, different thing. 37 CFR 1.142(a) provides that restriction is proper at any stage of prosecution up to final action. The confusion over the species to which the examiner is referring is moot in view of cancellation of these claims. Nevertheless, the examiner agrees, without prejudice, to examine all of the claims to the presently elected invention to the extent that they are directed to or encompassed by the embodiments of claims 46 and 61 as they now stand.

The requirement is still deemed proper and is therefore made FINAL.

Claims 10 and 12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the paper filed 11/21/2003.

Claims 16-75 are being examined.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 16-75 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The present invention provides isolated nucleic acid molecules comprising a polynucleotide encoding CAPP polypeptide having the amino acid sequence is shown in FIG. 1 (SEQ ID NO:2) or the amino acid sequence encoded by the cDNA clone deposited in a bacterial host as ATCC Deposit Number 97729 (page 3, lines 10-14). The present claims are directed to or encompass polynucleotides comprising the coding region of SEQ ID NO: 1 or polynucleotides encoding the amino acid sequence of SEQ ID NO: 2. The CAPP gene was discovered in an activated T-cell cDNA library (page 6, lines 3-5). The gene was identified by database distribution in activated T cells, CD34 positive cells, Ntera2 cells 14 days after RA stimulation, kidney cortex, adult heart, Jurkat cells and small intestine (page 10, lines 6-14). The present inventors have discovered that CAPP is highly expressed in adult heart, pancreas and placenta tissue (page 6, lines 9-10; page 38, lines 16-19). By Northern blot analysis it has been determined that this gene is abundant in adult heart and pancreas, with low amounts in placenta, lung, liver, skeletal muscle, kidney, spleen, thymus, prostate, testis, ovary, small intestine, colon and peripheral blood leukocytes (page 65, lines 11-15). The CAPP protein of the present invention shares sequence homology with Drosophila "brainiac" gene (FIG. 2) (SEQ ID NO:3) (page 8,

lines 23-24). FIG. 2 shows the regions of similarity between the amino acid sequences of the CAPP protein and Drosophila "brainiac" (page 8, lines 4-5). The CAPP protein shown in FIG. 1 (SEQ ID NO:2) is about 27.8% identical and about 48.4% similar to Drosophila "brainiac" protein. The present specification discloses that Brainiac interacts with the EGF receptor pathway in follicle cell development, citing Goode et al (Development 116:177-192 (1992)) (page 10, lines 20-24). Brainiac is a neurogenic secreted molecule that is believed to play a role in the differentiation of embryonic cells into neurons. Thus, the inventors contemplate that the CAPP polypeptide functions as a growth factor or similar cellular signaling polypeptide in vivo and that the CAPP polypeptide exerts an effect on the differentiation of cells in the early stages of cell and tissue development, and may serve to aid in the differentiation of embryonic cells into heart or pancreas cells. Page 47, lines 4-11. In addition, the present inventors have identified cDNA clones related to extensive portions of SEQ ID NO:1 (page 11, line 25, thorough page 12, line 10).

As best the examiner can determine, the basis for the assertion of CAPP functional activity is as follows:

CAPP is highly expressed in adult heart, pancreas and placenta tissue;

CAPP shares sequence homology with Drosophila brainiac;

brainiac interacts with the EGF receptor pathway in follicle cell development;

brainiac is a neurogenic secreted molecule that is believed to play a role in the differentiation of embryonic cells into neurons;

therefore, CAPP polypeptide exerts an effect on the differentiation of cells in the early stages of cell and tissue development, and may serve to aid in the differentiation of embryonic cells into heart or pancreas cells.

However, the specification provides no further characterization of CAPP expression in adult heart, pancreas and placenta tissue, or in any other tissue. As noted by Nathan (AS, cited by Applicants) many cytokines that subserve familiar functions postnatally play different or unknown roles embryologically and given the amino acid sequence of a cytokine and any of its actions one cannot predict when or where it will do what else (page 981, paragraph bridging columns 1-2). There is no evidence of record that any and/or all proteins expressed in adult heart, pancreas and placenta tissue could be used for any of the uses that applicants contemplate. Nor would one of skill in the art reasonably expect any and/or all proteins to be so useful. Accordingly, the significance of CAPP expression in adult heart, pancreas and placenta tissue, or in any other tissue is unknown.

Furthermore, one skilled in the art recognizes that although structural similarity can serve to classify a protein as related to other known proteins this classification is insufficient to establish a function or biological significance for the protein because ancient duplications and rearrangements of protein-coding segments have resulted in complex gene family relationships. Duplications can be tandem or dispersed and can involve entire coding regions or modules that correspond to folded protein domains. As a result, gene products may acquire new specificities, altered recognition properties, or modified functions. Extreme proliferation of some families within an organism, perhaps at the expense of other families, may correspond to functional innovations during

evolution. See Henikoff (AR, cited by Applicants), page 609, Abstract. Accordingly, although sequence identity may be indicative of some evolutionary relationship, it is not necessarily indicative of the ultimate identity and function of the compound. Homology or sequence identity is not predictive of, or an assurance of, preserved ultimate function for a related molecule. Rather, homology complements experimental data accumulated for the homologous protein in understanding the homologous protein's biological role. Although, the presence of a protein module in a protein of interest adds potential insight into its function and guides experiments, insight into the biological function of a protein cannot be automated. However, homology can be used to guide further research. See Henikoff (AR), paragraph bridging pages 613-614, through page 614, paragraph bridging columns 1-2. Accordingly, the significance of the present invention's similarity with brainiac is unknown.

The specification asserts that CAPP is a member of the muscle derived growth factor superfamily (Abstract) and that CAPP is a muscle derived growth factor (page 1, line 7). The expression of CAPP protein is expected to be necessary for the survival and maintenance of mature muscle cells, especially heart, placenta and pancreas tissue. Under certain conditions the CAPP protein is expected to act with other growth factors to modulate, e.g. block, the proliferation of mature heart and pancreas cells. Under certain conditions the CAPP protein is expected to act with other growth factors to program the differentiation of immature cells into cardiac or pancreatic cells. Paragraph bridging pages 5-6.

However, the specification acknowledges that in addition to their growth promoting and differentiation-inducing activities, growth factors elicit a wide variety of

effects in their target cells (page 2, lines 4-7). The search continues to exist for polypeptides that stimulate and/or inhibit growth of particular cells for both in vitro and in vivo uses (page 3, lines 1-4). There is no evidence of record that all growth factors are involved in survival and maintenance of mature muscle cells, modulating the proliferation of mature heart and pancreas cells, programming the differentiation of immature cells into cardiac or pancreatic cells, allowing mature muscle cells to replicate and divide, causing embryonic cells to differentiate into cardiac cells, and maintaining cell cultures of cardiac, pancreatic, or placental cells, nor that CAPP is involved in any of them. There is no evidence of record that a person of skill in the art would have appreciated that the identification of CAPP as a gene that is abundant in adult heart and pancreas, with low amounts in placenta, lung, liver, skeletal muscle, kidney, spleen, thymus, prostate, testis, ovary, small intestine, colon and peripheral blood leukocytes, without more, would have suggested any specific patentable utility. There is no evidence of record that a person of skill in the art would have appreciated that the low degree of homology between CAPP and Drosophila brainiac, without more, would have suggested any specific patentable utility. The specification provides no basis for concluding which, if any, of the widely varying growth factor activities is possessed by CAPP. Thus, a preponderance of the evidence of record shows that a person of skill in the art would not know how to use a protein based merely on its expression in adult heart, pancreas and placenta tissue and its sequence homology with Drosophila brainiac. The examiner therefore rejects the specification's assertion of utility of the presently claimed CAPP polynucleotides.

The specification asserts that CAPP gene expression and translation can be used as a marker to detect activated T-cells (page 6, lines 3-5) and that monitoring T cells activation is useful for a number of in vitro diagnostic purposes, including studying the effects of candidate drugs on the immune system, and determining whether the T cells of a subject have been activated by analyzing a blood sample taken from the subject or by assessing activity in an in vitro screening test. Page 38, lines 20-26.

Additionally, the specification asserts that since CAPP is highly expressed in mature heart, pancreas and placenta tissue, CAPP expression can be employed to determine the type of cells that are present in a cell culture. Page 38, lines 16-19.

By Northern blot analysis it has been determined that this gene is abundant in adult heart and pancreas, with low amounts in placenta, lung, liver, skeletal muscle, kidney, spleen, thymus, prostate, testis, ovary, small intestine, colon and peripheral blood leukocytes. The gene was identified by database distribution in activated T cells, CD34 positive cells, Ntera2 cells 14 days after RA stimulation, kidney cortex, adult heart, Jurkat cells and small intestine. Pages 64-65.

The specification asserts that isolated molecules, particularly DNA molecules, are useful as probes for gene mapping, by in situ hybridization with chromosomes, and for detecting expression of the CAPP gene in human tissue, for instance, by Northern blot analysis (page 12, lines 19-22).

Additionally, this CAPP gene expression can be employed as a marker to determine the presence of mature, terminally differentiated organ tissue, especially heart, pancreatic and placental tissue. Such a marker possesses practical utility in monitoring the growth of heart, pancreas and placental cells and tissues ex vivo. The effects of small

molecule drugs and polypeptide growth factors on the development of these cells and tissues can be assessed by monitoring the level of expression of the CAPP gene. Page 5, lines 25-31.

The specification also envisions that the nucleic acid molecules of the present invention are also valuable for chromosome identification. The sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome. Page 52, lines 4-6.

To employ the polynucleotide or polypeptide of the present invention as a tissue or chromosome marker is not a specific or substantial utility. All human proteins can invariably be classified into two categories -- those which are expressed in a tissue or developmental specific manner, and those which are not, or are expressed ubiquitously. It can be asserted that any protein that is expressed in a tissue specific manner can be used to detect the tissue in which it is expressed in a sample. Alternatively, a ubiquitously expressed human protein can be used to detect human tissue in a sample. Such utilities are analogous to the assertion that a particular protein can be employed as a molecular weight marker, which is neither a specific or substantial utility. Further, there is no evidence of record that CAPP expression is specific to an activated T cell. All viable resting and activated T cells would be expected to express many genes and their corresponding proteins which are required for cell viability and which are not required and/or not specific for the activated state. These genes and their corresponding proteins would be expected to be present in resting T cells, as well.

The specification envisions that for a number of disorders of smooth muscle tissue in the heart, pancreas or placenta, it is believed that significantly higher or lower levels of

CAPP gene expression can be detected in certain tissues (e.g., heart, pancreas and placenta) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" CAPP gene expression level, i.e., the CAPP expression level in tissue or bodily fluids from an individual not having a disorder of the heart, pancreas or placenta. Thus, the invention provides a diagnostic method useful during diagnosis of an internal organ disorder, wherein said disorder relates to the smooth muscle tissue of the heart, pancreas or placenta, which involves: (a) assaying CAPP gene expression level in cells or body fluid of an individual; (b) comparing the CAPP gene expression level with a standard CAPP gene expression level, whereby an increase or decrease in the assayed CAPP gene expression level compared to the standard expression level is indicative of one of said disorders. Page 6, lines 10-24.

An additional aspect of the invention is related to a method for treating an individual in need of an increased level of CAPP activity in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an isolated CAPP polypeptide of the invention or an agonist thereof. Page 7, lines 17-21.

A still further aspect of the invention is related to a method for treating an individual in need of a decreased level of CAPP activity in the body comprising, administering to such an individual a composition comprising a therapeutically effective amount of a CAPP antagonist. Preferred antagonists for use in the present invention are CAPP-specific antibodies. Page 7, lines 22-26.

It is believed that certain maladies in mammals may cause the mammals to express significantly altered levels of the CAPP protein and mRNA encoding the CAPP protein when compared to a corresponding "standard" mammal, i.e., a mammal of the same species not having the malady or condition. For example, a mammal suffering from pancreatitis or a condition that causes abnormal myocardial hypertrophy is expected to express altered levels of CAPP by the pancreas or heart, respectively. Further, it is believed that decreased levels of the CAPP protein can be detected in certain body fluids (e.g., sera, plasma, urine, and spinal fluid) from mammals with such a condition when compared to sera from mammals of the same species not having the condition. Thus, the invention provides a diagnostic method useful during diagnosis or pancreatitis or one of the many conditions that cause abnormal hypertrophy of the heart, such as hypertension, myocardial infarction, valve disease and cardiomyopathy. The method involves assaying the expression level of the gene encoding the CAPP protein in mammalian cells or body fluid and comparing the gene expression level with a standard CAPP gene expression level, whereby a decrease in the gene expression level over the standard is indicative of said conditions. Where a diagnosis has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting decreased CAPP gene expression will experience a worse clinical outcome relative to patients expressing the gene at a lower level. Paragraph bridging pages 37-38, through page 38, full paragraph 1.

To the extent that the specification relies upon CAPP expression in adult heart, pancreas and placenta tissue and its sequence homology with Drosophila brainiac to support such assertions of disease state diagnosis and prognosis utility, and to the extent

that a preponderance of the evidence of record shows that a person of skill in the art would not know how to use a protein based merely on its expression in adult heart, pancreas and placenta tissue and its sequence homology with Drosophila brainiac, as discussed above, then the examiner does not accept these assertions of disease state diagnosis and prognosis utility. There is no other evidence in the record supporting their assertion that CAPP would have been recognized as useful for disease state diagnosis and prognosis. The specification provides no other basis for concluding that CAPP is associated with any specific disease.

The present invention also provides a screening method for identifying compounds capable of enhancing or inhibiting a cellular response induced by the CAPP polypeptide, which involves contacting cells which express the CAPP polypeptide with the candidate compound, assaying a cellular response, and comparing the cellular response to a standard cellular response, the standard being assayed when contact is made in absence of the candidate compound; whereby, an increased cellular response over the standard indicates that the compound is an agonist and a decreased cellular response over the standard indicates that the compound is an antagonist. Page 7, lines 1-9.

In another aspect, a screening assay for agonists and antagonists is provided which involves determining the effect a candidate compound has on CAPP polypeptide modulation of cellular growth and differentiation. In particular, the method involves contacting a cell culture with CAPP polypeptide and a candidate compound and determining whether CAPP polypeptide increases or decreases cellular differentiation or proliferation in the presence of the candidate compound. Page 7, lines 10-16.

To the extent that the specification relies upon CAPP expression in adult heart, pancreas and placenta tissue and its sequence homology with Drosophila brainiac to support such assertions of a cellular responses induced by the CAPP, and to the extent that a preponderance of the evidence of record shows that a person of skill in the art would not know how to use a protein based merely on its expression in adult heart, pancreas and placenta tissue and its sequence homology with Drosophila brainiac, as discussed above, then the examiner does not accept these assertions of CAPP cellular responses. There is no other evidence in the record supporting their assertion that CAPP would have been recognized as useful in such screening procedures. The specification provides no other basis for concluding that CAPP is associated with any specific cellular response.

The present application is directed to nucleic acid molecules at least 90%, 95%, 96%, 97%, 98% or 99% identical to the nucleic acid sequence shown in FIG. 1 (SEQ ID NO:1) or to the nucleic acid sequence of the deposited cDNA, irrespective of whether they encode a polypeptide having CAPP activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having CAPP activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid molecules of the present invention that do not encode a polypeptide having CAPP activity include, inter alia, (1) isolating the CAPP gene or allelic variants thereof in a cDNA library; (2) in situ hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide precise chromosomal location of the CAPP gene. Paragraph bridging pages 18-19. By "a polypeptide having CAPP activity" is intended polypeptides exhibiting

activity similar, but not necessarily identical, to an activity of the CAPP protein of the invention (either the full-length protein or, preferably, the mature protein), as measured in a particular biological assay. Thus, "a polypeptide having CAPP protein activity" includes polypeptides that exhibit CAPP activity. Paragraph bridging pages 18-19.

However, materials to be used for research, or methods of using those materials for research, raise issues of whether the utilities require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use. See, e.g., Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966) wherein a research utility was not considered a "substantial utility."

The specification discloses that the polypeptide of the present invention could be used as a molecular weight marker on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art (page 31, lines 29-31). "Throw away" utilities do not meet the tests for a specific or substantial utility. Using a polypeptide as a molecular weight marker is a utility that is not specific (essentially and/or all polypeptides could function as molecular weight markers). Use of any protein as a molecular weight marker is "throw away" utility that would not pass muster as a specific or substantial utility under 35 U.S.C. §101.

The specification discloses that the polypeptides of the present invention can also be used to raise polyclonal and monoclonal antibodies, which are useful in assays for detecting CAPP protein expression as described below or as agonists and antagonists capable of enhancing or inhibiting CAPP protein function (page 32, lines 1-8). However, in the absence of a specific and substantial use or well established use for the CAPP

polynucleotide or CAPP polypeptide there is no specific and substantial use or well established use for antibodies that bind the CAPP polypeptide.

The inventors contemplate that the CAPP polypeptide functions as a growth factor or similar cellular signaling polypeptide in vivo. CAPP possesses homology to the Drosophila brainiac polypeptide. This polypeptide is a neurogenic secreted molecule that is believed to play a role in the differentiation of embryonic cells into neurons. Thus, it is contemplated that the CAPP polypeptide exerts an effect on the differentiation of cells in the early stages of cell and tissue development, and may serve to aid in the differentiation of embryonic cells into heart or pancreas cells. Page 47, lines 4-11.

The CAPP polypeptide is also highly expressed in adult heart and pancreas tissue. One role of CAPP in mature muscle tissue may be to inhibit cell replication and division in the mature muscle tissue. Page 47, lines 12-14.

Thus, the inventors contemplate a number of additional practical utilities that use the growth-effecting properties of the CAPP polypeptide to module the differentiation and proliferation of cells and tissue, both in vivo and ex vivo. Page 47, lines 15-17.

Assessing the modulating effects of the CAPP polypeptide on the cellular proliferation and differentiation of cells can be performed as described below. Biological activity of CAPP polypeptides can be examined in organ culture assays or in colony assay systems in agarose culture. Stimulation or inhibition of cellular proliferation may be measured by a variety of assays. For observing cell growth inhibition, one can use a solid or liquid medium. In a solid medium, cells undergoing growth inhibition can easily be selected from the subject cell group by comparing the sizes of colonies formed. In a

liquid medium, growth inhibition can be screened by measuring culture broth turbidity or incorporation of labeled thymidine into DNA. Paragraph bridging pages 47-48.

Effect upon cellular differentiation can be measured by contacting embryonic cells with various amounts of a CAPP polypeptide and observing the effect upon differentiation of the embryonic cells. Tissue specific antibodies and microscopy may be used to identify the resulting cells. Page 48, lines 8-11.

However, to the extent that the specification relies upon CAPP expression in adult heart, pancreas and placenta tissue and its sequence homology with Drosophila brainiac to support such assertions of therapeutic or cell culture uses, and to the extent that a preponderance of the evidence of record shows that a person of skill in the art would not know how to use a protein based merely on its expression in adult heart, pancreas and placenta tissue and its sequence homology with Drosophila brainiac, as discussed above, then the examiner does not accept these assertions of therapeutic or cell culture uses. There is no other evidence in the record supporting the assertion that CAPP would have been recognized as useful for such therapeutic or cell culture uses. The specification provides no other basis for concluding that CAPP is associated with any specific disease or cellular response. Furthermore, measuring an unspecified response or condition is an example of a situation that requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, does not define a "substantial utility."

In addition, Zhou (U) (Proc Natl Acad Sci U S A. 2000 October 10; 97 (21): 11673-5) as evidenced by Zhou (AS, cited by Applicants) discloses an isolated nucleic acid molecule that comprises a nucleotide sequence that is identical to nucleotides 233-

1423 of the present application's SEQ ID NO: 1 and that encodes a polypeptide comprising an amino acid sequence that is identical to the present application's SEQ ID NO: 2, as indicated below (Qy = SEQ ID NO: 1 or SEQ ID NO: 2, as appropriate) (Db = Zhou's nucleic acid sequence or amino acid sequence, as appropriate):

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  Query Match             100.0%;  Score 1191;  DB 9;  Length 1831;
  Best Local Similarity   100.0%;  Pred. No. 0;
  Matches 1191;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 ATGAGTGTTGGACGTCGAAGAATAAAGTTGTTGGGTATCCTGATGATGGCAAATGTCTTC 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        236 ATGAGTGTTGGACGTCGAAGAATAAAGTTGTTGGGTATCCTGATGATGGCAAATGTCTTC 295

Qy         61 ATTTATTTTATTATGGAAGTCTCCAAAAGCAGTAGCCAAGAAAAAAATGGAAAAGGGGAA 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        296 ATTTATTTTATTATGGAAGTCTCCAAAAGCAGTAGCCAAGAAAAAAATGGAAAAGGGGAA 355

Qy        121 GTAATAATACCCAAAGAGAAGTTCTGGAAGATATCTACCCCTCCCGAGGCATACTGGAAC 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        356 GTAATAATACCCAAAGAGAAGTTCTGGAAGATATCTACCCCTCCCGAGGCATACTGGAAC 415

Qy        181 CGAGAGCAAGAGAAGCTGAACCGGCAGTACAACCCCATCCTGAGCATGCTGACCAACCAG 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        416 CGAGAGCAAGAGAAGCTGAACCGGCAGTACAACCCCATCCTGAGCATGCTGACCAACCAG 475

Qy        241 ACGGGGGAGGCGGGCAGGCTCTCCAATATAAGCCATCTGAACTACTGCGAACCTGACCTG 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        476 ACGGGGGAGGCGGGCAGGCTCTCCAATATAAGCCATCTGAACTACTGCGAACCTGACCTG 535

Qy        301 AGGGTCACGTCGGTGGTTACGGGTTTTAACAACTTGCCGGACAGATTTAAAGACTTTCTG 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        536 AGGGTCACGTCGGTGGTTACGGGTTTTAACAACTTGCCGGACAGATTTAAAGACTTTCTG 595

Qy        361 CTGTATTTGAGATGCCGCAATTATTCACTGCTTATAGATCAGCCGGATAAGTGTGCAAAG 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        596 CTGTATTTGAGATGCCGCAATTATTCACTGCTTATAGATCAGCCGGATAAGTGTGCAAAG 655

Qy        421 AAACCTTTCTTGTTGCTGGCGATTAAGTCCCTCACTCCACATTTTGCCAGAAGGCAAGCA 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        656 AAACCTTTCTTGTTGCTGGCGATTAAGTCCCTCACTCCACATTTTGCCAGAAGGCAAGCA 715

Qy        481 ATCCGGGAATCCTGGGGCCAAGAAAGCAACGCAGGGAACCAAACGGTGGTGCGAGTCTTC 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        716 ATCCGGGAATCCTGGGGCCAAGAAAGCAACGCAGGGAACCAAACGGTGGTGCGAGTCTTC 775

Qy        541 CTGCTGGGCCAGACACCCCCAGAGGACAACCACCCCGACCTTTCAGATATGCTGAAATTT 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        776 CTGCTGGGCCAGACACCCCCAGAGGACAACCACCCCGACCTTTCAGATATGCTGAAATTT 835

Qy        601 GAGAGTGAGAAGCACCAAGACATTCTTATGTGGAACTACAGAGACACTTTCTTCAACTTG 660
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        836 GAGAGTGAGAAGCACCAAGACATTCTTATGTGGAACTACAGAGACACTTTCTTCAACTTG 895

Qy        661 TCTCTGAAGGAAGTGCTGTTTCTCAGGTGGGTAAGTACTTCCTGCCCAGACACTGAGTTT 720
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        896 TCTCTGAAGGAAGTGCTGTTTCTCAGGTGGGTAAGTACTTCCTGCCCAGACACTGAGTTT 955

Qy        721 GTTTTCAAGGGCGATGACGATGTTTTTGTGAACACCCATCACATCCTGAATTACTTGAAT 780
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        956 GTTTTCAAGGGCGATGACGATGTTTTTGTGAACACCCATCACATCCTGAATTACTTGAAT 1015

Qy        781 AGTTTATCCAAGACCAAAGCCAAAGATCTCTTCATAGGTGATGTGATCCACAATGCTGGA 840
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1016 AGTTTATCCAAGACCAAAGCCAAAGATCTCTTCATAGGTGATGTGATCCACAATGCTGGA 1075

Qy        841 CCTCATCGGGATAAGAAGCTGAAGTACTACATCCCAGAAGTTGTTTACTCTGGCCTCTAC 900
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1076 CCTCATCGGGATAAGAAGCTGAAGTACTACATCCCAGAAGTTGTTTACTCTGGCCTCTAC 1135

Qy        901 CCACCCTATGCAGGGGGAGGGGGGTTCCTCTACTCCGGCCACCTGGCCCTGAGGCTGTAC 960
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Db       1136 CCACCCTATGCAGGGGGAGGGGGGTTCCTCTACTCCGGCCACCTGGCCCTGAGGCTGTAC 1195

Qy        961 CATATCACTGACCAGGTCCATCTCTACCCCATTGATGACGTTTATACTGGAATGTGCCTT 1020
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1196 CATATCACTGACCAGGTCCATCTCTACCCCATTGATGACGTTTATACTGGAATGTGCCTT 1255

Qy       1021 CAGAAACTCGGCCTCGTTCCAGAGAAACACAAAGGCTTCAGGACATTTGATATCGAGGAG 1080
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1256 CAGAAACTCGGCCTCGTTCCAGAGAAACACAAAGGCTTCAGGACATTTGATATCGAGGAG 1315

Qy       1081 AAAAACAAAAATAACATCTGCTCCTATGTAGATCTGATGTTAGTACATAGTAGAAAACCT 1140
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1316 AAAAACAAAAATAACATCTGCTCCTATGTAGATCTGATGTTAGTACATAGTAGAAAACCT 1375

Qy       1141 CAAGAGATGATTGATATTTGGTCTCAGTTGCAGAGTGCTCATTTAAAATGC 1191
              |||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1376 CAAGAGATGATTGATATTTGGTCTCAGTTGCAGAGTGCTCATTTAAAATGC 1426

  Query Match           100.0%;  Score 2123;  DB 13;  Length 397;
  Best Local Similarity  100.0%;  Pred. No. 1.1e-208;
  Matches  397;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 MSVGRRRIKLLGILMMANVFIYFIMEVSKSSSQEKNGKGEVIIPKEKFWKISTPPEAYWN 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MSVGRRRIKLLGILMMANVFIYFIMEVSKSSSQEKNGKGEVIIPKEKFWKISTPPEAYWN 60

Qy         61 REQEKLNRQYNPILSMLTNQTGEAGRLSNISHLNYCEPDLRVTSVVTGFNNLPDRFKDFL 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 REQEKLNRQYNPILSMLTNQTGEAGRLSNISHLNYCEPDLRVTSVVTGFNNLPDRFKDFL 120

Qy        121 LYLRCRNYSLLIDQPDKCAKKPFLLLAIKSLTPHFARRQAIRESWGQESNAGNQTVVRVF 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 LYLRCRNYSLLIDQPDKCAKKPFLLLAIKSLTPHFARRQAIRESWGQESNAGNQTVVRVF 180

Qy        181 LLGQTPPEDNHPDLSDMLKFESEKHQDILMWNYRDTFFNLSLKEVLFLRWVSTSCPDTEF 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 LLGQTPPEDNHPDLSDMLKFESEKHQDILMWNYRDTFFNLSLKEVLFLRWVSTSCPDTEF 240

Qy        241 VFKGDDDVFVNTHHILNYLNSLSKTKAKDLFIGDVIHNAGPHRDKKLKYYIPEVVYSGLY 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 VFKGDDDVFVNTHHILNYLNSLSKTKAKDLFIGDVIHNAGPHRDKKLKYYIPEVVYSGLY 300

Qy        301 PPYAGGGGFLYSGHLALRLYHITDQVHLYPIDDVYTGMCLQKLGLVPEKHKGFRTFDIEE 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 PPYAGGGGFLYSGHLALRLYHITDQVHLYPIDDVYTGMCLQKLGLVPEKHKGFRTFDIEE 360

Qy        361 KNKNNICSYVDLMLVHSRKPQEMIDIWSQLQSAHLKC 397
              |||||||||||||||||||||||||||||||||||||
Db        361 KNKNNICSYVDLMLVHSRKPQEMIDIWSQLQSAHLKC 397
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Zhou (AS) discloses that the human cDNA encodes a β-1,3-N-acetylglucosaminyltransferase (β3GnT). The human cDNA included an ORF coding for predicted type II transmembrane polypeptide. The β3GnT gene was widely expressed in human and mouse tissues, although differences in the transcript levels were visible, thus indicating possible tissue-specific regulation mechanisms. See the Abstract. However, the instant specification does not disclose that CAPP is an enzyme. In addition, Zhou (U) as evidenced by Zhou (AS) does not suggest that β3GnT would have been understood by those skilled in the art to imply that β3GnT was useful for any particular purpose the present specification contemplates.

A patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. At the time of Applicants' invention the work required to confer value on CAPP, however, remained to be done. The instant specification's CAPP-specific disclosure does not justify a grant of patent rights. See Brenner, 383 U.S. at 534, 148 USPQ at 695: "[A] process patent in the chemical field, which has not been developed and pointed to the degree of specific utility, creates a monopoly of knowledge which should be granted only if clearly commanded by the statute. Until the process claim has been reduced to production of a product shown to be useful, the metes and bounds of that monopoly are not capable of precise delineation. It may engross a vast, unknown, and perhaps unknowable area. Such a patent may confer power to block off whole areas of scientific development."

Claims 16-75 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 46-75 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 46-60 are drawn to or encompass polynucleotides at least 95% identical to polynucleotides encoding the amino acid sequence of SEQ ID NO: 2 or some portion thereof. Claims 61-75 are drawn to or encompass polynucleotides encoding polypeptides having at least 95% amino acid sequence identity to SEQ ID NO: 2 or some portion thereof. The present application is directed to nucleic acid molecules at least 90%, 95%, 96%, 97%, 98% or 99% identical to the nucleic acid sequence shown in FIG. 1 (SEQ ID NO:1) or to the nucleic acid sequence of the deposited cDNA, irrespective of whether they encode a polypeptide having CAPP activity (page 18, lines 19-22). The CAPP of the present invention may include one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation (page 28, lines 19-21). There is no functional limitation in the claims. The claims do not require that the polynucleotides or polypeptides possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polynucleotides encoding a genus of polypeptides that is defined only by sequence identity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any

combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genera, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polynucleotides encoding the amino acid sequence of SEQ ID NO: 2, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 46-75 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to or encompass the genus of all polynucleotides at least 95% identical to the genus of all polynucleotides encoding the amino acid sequence of SEQ ID NO: 2 or some portion thereof. The claims are directed to or encompass the genus of all polynucleotides encoding the genus of all polypeptides at least 95% identical to SEQ ID NO: 2 or some portion thereof. The present application is directed to nucleic acid molecules at least 90%, 95%, 96%, 97%, 98% or 99% identical to the nucleic acid sequence shown in FIG. 1 (SEQ ID NO:1) or to the nucleic acid sequence of the deposited cDNA, irrespective of whether they encode a polypeptide having CAPP activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having CAPP activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Paragraph bridging pages 18-19.

There is no functional limitation in the claims, and the utility of the degenerate polynucleotides is in the production of the encoded polypeptide. The specification provides no information regarding the occurrence of these degenerate polynucleotides in nature and their use as probes or primers and it is unpredictable which of those degenerate sequences, if any, would be useful as probes or primers. The claim encompasses an unreasonable number of inoperative embodiments, which the skilled artisan would not know how to use. In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor, it would require undue experimentation for the skilled artisan to make and/or use the full scope of the claimed invention.

Claims 33-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ novel nucleic acid molecules, i.e., ATCC deposit No. 97729. Since the nucleic acid molecules are essential to the claimed invention they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. If the nucleic acid molecules are not so obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the nucleic acid molecules. The specification does not disclose a repeatable process to obtain the nucleic acid molecules and it is not apparent if the nucleic acid molecules are

readily available to the public. It is noted that Applicant has deposited the nucleic acid molecules (p. 12 of the specification), but there is no indication in the specification as to public availability. If the deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific nucleic acid molecules have been deposited under the Budapest Treaty and that the nucleic acid molecules will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. §§ 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit will be made (see 37 C.F.R. § 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

Applicant's attention is directed to M.P.E.P. §2400 in general, and specifically to §2411.05, as well as to 37 C.F.R. § 1.809(d), wherein it is set forth that "the specification shall contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited material sufficient to specifically identify it and to permit examination." At p. 12, the address of the depository is missing. The specification should be amended to include such, however, Applicant is cautioned to avoid the entry of new matter into the specification by adding any other information. The new address for the ATCC, effective March 23, 1998, is:

American Type Culture Collection
10801 University Boulevard
Manassas, VA 20110-2209.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 47-49, 62-64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 47-49, 62-64 recite the limitation "said second nucleotide sequence." There is insufficient antecedent basis for this limitation in the claim.

Conclusion

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON

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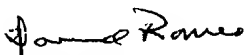

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
MARCH 16, 2004